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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,088	12/05/2003	Martinus Bernardus Vrouenraets	2344-40	8108

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NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	PAPER NUMBER
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/18/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/980,088	VROUENRAETS ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-11 and 14-18* is/are pending in the application.

4a) Of the above claim(s) *11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 5-10 and 14-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/16/2007 has been entered.

Claims 1, 3, 5-11 and 14-18 are currently pending.

Claim 11 is withdrawn from consideration as being drawn to a non-elected invention.

Claims 1, 3, 5-10 and 14-18 are currently under consideration.

Claim Objections

Claim 16 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case, claim 16 recites "[T]he compound according to claim 7, where VIII represents p-THPC or o-THPC." However, claim 7 depends from claim 1 which already sets forth that the ring structure of (VIII) carries four *m*-hydroxy phenyl groups. As such, independent claim 1 has already set forth the limitation that the hydroxyl groups have to be in the *meta* position and not the *ortho* or *para* positions.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 3, 5-10 and 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bonnet et al. (US Patent 4,992,257, 1991, IDS, *of record*) in view of Latouche et al. (Tetrahedron Letters 1995; 36: 1664-1666, IDS, *of record*) and Mauclaire et al. (US Patent 5,268,371, 1993, *of record*) and in further view of Westerman et al. (Int. J. Cancer 1998; 76: 842-850, *of record*).

Bonnet et al. teach (column 8, lines 37-68) dihydro and tetra-hydro porphyrins (referred to as chlorins and bacteriochlorins respectively, column 6, lines 21-24) having four aromatic phenyl substituted rings carrying one or more hydroxyl groups, wherein the hydroxyl groups may be in the *ortho*, *para* or *meta* position. With regards to the dihydro and tetra-hydro porphyrins, the patent teaches that the dihydro and tetra-hyrdro porphyrins include, but are not limited to, p-THPC, m-THPC, o-THPC and m-THPBC (column 6, Table 2). Bonnet et al. further teach (column 1, line 65 to column 2, line 1) that the compounds can be used as a form of cancer therapy, wherein the compound is administered to locate the tumor followed by illumination of the tumor with light of a wavelength absorbed by the compound.

Bonnet et al. do not explicitly teach that the dihydro and tetra-hydro porphyrins (referred to as chlorines and bacteriochlorins respectively, column 6, lines 21-24) having four aromatic phenyl substituted rings carrying one or more hydroxyl groups are in turn linked to an antibody against a cell surface antigen of cancer cells. Nor does Bonnet et al. teach that the antibody and porphyrin derivatives are linked via an ether linkage through a COOH group.

Westermann et al. teach (page 842, 2nd column, 1st full paragraph) that the major disadvantages of m-THPC phototherapy include, but are limited to, a relatively low tumor selectivity which, in view of the strong photoxic properties, can lead to undesired side effects in adjacent normal tissues. As a way to circumvent this disadvantage, the reference teaches a conjugate comprising the photosensitizer metal-tetrahydroxyphenylchlorin (m-THPC) conjugated to

polyethylene glycol which preserves its function of phototherapy and represents an interesting first step in favor of the strategy of conjugating photosensitizing dyes to anti-tumor antibodies (page 849, 2nd column, 2nd paragraph).

Mauclaire et al. teach derivatives of porphyrins and metalloporphyrins conjugated to a biologically active molecule (Title). With regards to the biologically active molecule, the patent teaches (column 8, lines 66-68 and column 9, lines 33-34) that such biologically active molecules include, but are limited to, antibodies, wherein the antibodies are directed against a cell surface antigen of the cancer cells. Specifically, Mauclaire et al. teach (column 5, lines 38-53) that the presence of the COOH group on the porphyrin gives them the property of being covalently bondable to biologically active molecules such as antibodies.

Latouche et al. disclose porphyrin derivatives having four aromatic phenyl substituted Ar's carrying one or more hydroxyl groups suitably linked via a ether linkage to a carboxyl group, e.g., COOH (compound shown on page 1665). The reference further teaches (page 1665, 1st paragraph, lines 3-5) that radiolabelled metalloporphyrins have significantly improved the efficacy of porphyrins for tumor detection, wherein the method can be improved by associating a radioactive metal complex and an antibody in order to deliver the reagent to a specific target. Moreover, Latouche et al. teach that the specific insertion of the metal in the porphyrin even in the presence of a good copper chelator like bovine albumin allows preliminary coupling of these ortho substituted porphyrins with antibodies before ^{64}Cu insertion (page 1666, lines 13-15).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to modify m-THPC as taught by Bonnet et al. with an antibody in view of the teachings of Westerman et al. and Mauclaire et al.. One would have been motivated to do so because Westerman et al. teach that one of the major disadvantages with m-THPC phototherapy is the lower tumor selectivity that leads to undesirable side effects. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying m-THPC as taught by Bonnet et al. with an antibody in view of the teachings of Westerman et al. and Mauclaire et al, one would achieve a method of specifically targeting m-THPC to tumor cells. Moreover, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have

been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).

In addition, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to modify m-THPC as taught by Bonnet et al. so that an antibody is linked to the hydroxyl group through an ether linking group such as $-CH_2C(O)OH$ in view of the teachings of Latouche et al. and Mauclaire et al.. One would have been motivated to do so because Latouche et al. provides the synthesis of $CH_2C(O)OH$ ether containing porphyrins and Mauclaire et al. teach that the presence of COOH groups of porphyrins gives them the property of being covalently bondable to biologically active molecules such as antibodies. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by modifying m-THPC as taught by Bonnet et al. so that an antibody is linked to the hydroxyl group through an ether linking group such as $-CH_2C(O)OH$ in view of the teachings of Latouche et al. and Mauclaire et al., one would achieve a covalently bondable –COOH group on m-THPC which can be linked to an antibody for specific tumor localization of m-THPC.

In response to this rejection, Applicants submit that Bonnett discloses the synthesis of dihydroporphyrins, but makes no mention of or suggestion of the use of monoclonal antibodies. Applicants further submit that Mauclaire is not relevant because it deals with the problem of linking monoclonal antibodies by providing a single phenyl group R_2 around the porphyrin ring, the remaining three R1 groups being pyrindyl radicals. Thus, Applicants assert that the person of ordinary skill would understand from the Mauclaire reference that to avoid problems of cross-linking antibodies, only a single functional group around the porphyrin should be used. In contrast, Applicants assert that the present invention involves a novel experimental protocol (set out in Figure 1) involving activated TFP groups, which allows the control of the number of monoclonal antibodies linked to the 4-fucntional porphyrin rings and eventually to arrive at the antibody conjugate. Moreover, Applicants assert that Westermann discloses an old method for coupling porphyrins to a polyethylene glycol, but there is no disclosure or suggestion of coupling monoclonal antibodies. In addition, Applicants assert that while Westermann indicates that this observation represents "an interesting first step in favor of the strategy of conjugating photosensitizing dyes to anti-tumor antibodies", this is not a disclosure which would lead one of ordinary skill to the present invention based on the cited art combination.

These arguments have been carefully considered, but are not found persuasive.

In response to Applicants arguments to the references individually not teaching the claimed invention, the Examiner recognizes that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It is the combination of all of the cited and relied upon references which make up the state of the art with regard to the claimed invention. Furthermore, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). There is no requirement that an "express, written motivation to combine must appear in prior art references before a finding of obviousness." See Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1276, 69 USPQ2d 1686, 1690 (Fed. Cir. 2004). For example, motivation to combine prior art references may exist in the nature of the problem to be solved (Ruiz at 1276, 69 USPQ2d at 1690) or the knowledge of one of ordinary skill in the art (National Steel Car v. Canadian Pacific Railway Ltd., 357 F.3d 1319, 1338, 69 USPQ2d 1641, 1656 (Fed. Cir. 2004)). In the instant case, those of skill in the art would recognize that while m-THPC is useful for the treatment of cancer as taught by Bonnet et al., a major disadvantage of m-THPC phototherapy is the lower tumor selectivity that leads to undesirable side effects as taught by Westerman. As such, the problem to be solved is improving the tumor selectivity of m-THPC, wherein it is well known in the art that porphyrin derivatives can be conjugated to biologically active molecules such as antibodies directed against a cell surface antigen of the cancer cells in view of the teachings of Mauclaire et al.. Thus, the references are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). Therefore, one of ordinary skill in the art would have a reasonable expectation of success that by modifying m-THPC as taught by Bonnet et al. with an antibody in view of the teachings of Westerman et al. and Mauclaire et al, one would achieve a method of specifically targeting m-THPC to tumor cells. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., an activated TFP group) are not recited in the rejected

claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). As such, this argument has not been considered.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bonnet et al. (US Patent 4,992,257, 1991, IDS, *of record*) in view of Westerman et al. (Int. J. Cancer 1998; 76: 842-850, *of record*), Latouche et al. (Tetrahedron Letters 1995; 36: 1664-1666, IDS, *of record*) and Mauclaire et al. (US Patent 5,268,371, 1993, *of record*) and in further view Bendig et al. (WO 92/15683, 1992, *of record*).

Bonnet et al. in view of Westerman et al. (Int. J. Cancer 1998; 76: 842-850), Latouche et al. (Tetrahedron Letters 1995; 36: 1664-1666, IDS) and Mauclaire et al. (US Patent 5,268,371, 1993) teach (column 8, lines 37-68), as applied to claims 1, 3, 5-10 and 15-18 above, m-THPC linked to an antibody directed against cell surface antigens of cancer or other diseased cells, wherein the antibody is linked to the aromatic hydroxyl group though a ether linking group containing a –COOH.

Bonnet et al. in view of Westerman et al. (Int. J. Cancer 1998; 76: 842-850), Latouche et al. (Tetrahedron Letters 1995; 36: 1664-1666, IDS) and Mauclaire et al. (US Patent 5,268,371, 1993) do not explicitly teach that the antibody is mMAb 425.

Bendig et al. teach that murine monoclonal antibody 425 (Mab 425) binds to a polypeptide epitope on the external domain of the human epidermal growth factor receptor and inhibits the binding of epidermal growth factor at both low and high affinity EGFR sites (page 3, lines 7-12). Moreover, Bendig et al. teach that enhanced expression of EGFR is found to occur on malignant tissues from a variety of sources, thus making mAb 425 a useful agent for the diagnosis and therapeutic treatment of human tumors (page 3, lines 12-21).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to conjugate mAb 425 to the porphyrin derivatives taught by Bonnet et al. in view of Westerman et al. (Int. J. Cancer 1998; 76: 842-850), Latouche et al. (Tetrahedron Letters 1995; 36: 1664-1666, IDS) and Mauclaire et al. (US Patent 5,268,371, 1993) in further view of Bendig's teachings that mAb 425 is a useful agent for the diagnosis and treatment of human tumors due to EGFR's enhanced expression in a variety of tumors. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by conjugating mAb 425 to the porphyrin

derivatives, one would achieve a porphyrin:mAb 425 immunoconjugate useful for the treatment or diagnosis of tumors characterized by enhanced EGFR expression.

Therefore, No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Patent Examiner
Art Unit 1642

BF

SHANON FOLEY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600